Right but not left ventricular function recovers early after living-donor lobar lung transplantation in patients with pulmonary arterial hypertension

Shinichi Toyooka, MD,[a] Kengo Fukushima Kusano, MD,[b] Keiji Goto, MD,[c] Yamane Masaomi, MD,[a] Takahiro Oto, MD,[a] Yoshifumi Sano, MD,[a] Soichiro Fuke, MD,[b] Megumi Okazaki, RN,[a] Toru Ohe, MD,[b] Shingo Kasahara, MD,[d] Shunji Sano, MD,[d] and Hiroshi Date, MD[e]

Objective: The aim of this study was to evaluate right and left ventricular functions in patients with pulmonary arterial hypertension after living-donor lobar lung transplantation compared with those without hypertension.

Methods: Thirty-three recipients of living-donor lobar lung transplantation were divided into two groups: those with pulmonary arterial hypertension (PAH group; n = 12) and those without (non-PAH group; n = 21). Their systolic pulmonary artery pressure was 93.1 ± 6.7 mm Hg versus 31.4 ± 2.9 mm Hg, respectively. Right and left ventricular ejection fractions, systolic pulmonary artery pressure, and cardiac index were serially measured by radionuclide ventriculography and right heart catheterization, respectively.

Results: Pretransplant right and left ventricular ejection fractions were lower in the PAH group (29.8% ± 7.0%, 49.9% ± 6.6%) than in the non-PAH group (49.7% ± 3.3%, 65.2% ± 1.9%) ($P = .010, .068$). Two months after living-donor lobar lung transplantation, right ventricular ejection fraction and systolic pulmonary artery pressure in the PAH group (57.3% ± 5.1%, 25.7 ± 1.8 mm Hg) improved dramatically, equal to those in the non-PAH group. In contrast, left ventricular ejection fraction and cardiac index in the PAH group (50.9% ± 3.7%, 2.66 ± 0.12 L · min^{-1} · m^{-2}) were still significantly lower than in the non-PAH group (65.4% ± 2.8%, 3.13 ± 0.15 L · min^{-1} · m^{-2}) ($P = .0038, .037$). At 6 to 12 months, the PAH group demonstrated a significant rise in left ventricular ejection fraction and cardiac index that reached similar values in the non-PAH group measured at 2 months. These values were stable for up to 3 years.

Conclusions: Right ventricular function recovered early after living-donor lobar lung transplantation in the PAH group. In contrast, recovery of left ventricular function required 6 to 12 months. Improved cardiac function was sustained for up to 3 years, suggesting long-term durability of cardiac function recovery after living-donor lobar lung transplantation.

Lung transplantation has been performed as an effective treatment for various kinds of pulmonary disease. Living-donor lobar lung transplantation (LDLLT) was developed at Stanford University and has been established at the University of Southern California as a safe and reproducible procedure to deal with the shortage of cadaveric donors.[1] LDLLT has been used in patients with a variety of end-stage pulmonary diseases, including pulmonary arterial hypertension (PAH), who are too ill to wait for cadaveric lung transplantation.[2] PAH is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance. Consequently, right ventricular enlargement with hypertrophy occurs, and the enlarged right ventricle, by compressing the left ventricle, limits its volume and results in severe pump dysfunction. Three classes of medications have now shown efficacy in the treatment of PAH: prostanoids,[3,4] endothelin receptor antagonists,[5] and phosphodiesterase-5 inhibitors.[6] When all these medical treatments fail, lung transplantation remains the treatment of last resort.

From January 2000, we began to apply LDLLT to both pediatric[7] and adult[8] patients with PAH. Recently, we[9] reported excellent clinical outcomes of LDLLT for 11 patients with PAH for whom mortality was likely to be high without lung transplantation. Although a limited amount of lung tissue was implanted, pulmonary artery pressure (PAP) normalized soon after LDLLT.

It has been clearly shown that a significant improvement in right ventricular function occurs after single or double lung transplantation in patients with PAH.[10-13] In contrast, left ventricular recovery has not been well studied. Furthermore, little is known about right and left ventricular functions after LDLLT in which a limited amount of lung

From the Departments of Cancer and Thoracic Surgery,[a] Cardiovascular Medicine,[b] Anesthesiology and Resuscitology,[c] Cardiovasuclar Surgery,[d] Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; and the Department of Thoracic Surgery,[e] Kyoto University Graduate School of Medicine, Kyoto, Japan.

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Address for reprints: Hiroshi Date, MD, Department of Thoracic Surgery, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-Cho, Sakyo-Ku, Kyoto 606-8507, Japan (E-mail: hdate@kuhp.kyoto-u.ac.jp).

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Abbreviations and Acronyms

CI = cardiac index
FVC = forced vital capacity
LDLLT = living-donor lobar lung transplantation
LVEF = left ventricular ejection fraction
PAH = pulmonary arterial hypertension
PAP = pulmonary artery pressure
RVEF = right ventricular ejection fraction
sPAP = systolic pulmonary artery pressure

tissue is implanted. For this purpose, we serially measured right and left ventricular functions of patients with PAH receiving LDLLT and compared them to those of patients without PAH.

PATIENTS AND METHODS

Recipient and Donor Selection

All recipients fulfilled the criteria for conventional bilateral lung transplantation. We have accepted only critically ill patients as candidates for LDLLT and only relatives within the second degree or a spouse as living donors. Each case was carefully reviewed by the Lung Transplant Evaluation Committee at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. Regarding size matching, we[14] have previously proposed a formula to estimate the forced vital capacity (FVC) of the graft on the basis of the donor's measured FVC and the number of pulmonary segments implanted. We accepted the size disparity when the total FVC of the 2 grafts was more than 45% of the predicted FVC of the recipient for non-PAH and when it was more than 50% for PAH.

Surgical Procedures

The surgical aspects of LDLLT have been described previously.[14] The right and left lower lobes were removed from 2 healthy donors. These 2 lobes were then implanted in the recipient under cardiopulmonary bypass as whole right and left lungs. Just before reperfusion, 500 mg to 1 g of methylprednisolone was administered intravenously, and nitric oxide inhalation was initiated at 20 ppm. To maintain patients' nutritional status and for perioperative drug delivery, we inserted a nasal feeding tube to the proximal jejunum at the conclusion of the operation.

Postoperative Management of the Recipient

The patient was kept intubated for at least 3 days to maintain optimal expansion of the lobes. Weaning from a ventilator was intentionally slow, and tracheostomy was performed when patients showed any signs of sputum retention. Postoperative immunosuppression consisted of triple-drug therapy under a previously described protocol. Three months after LDLLT, patients were allowed to return to their home town. Routine full postoperative assessment was performed at 6 months, 12 months, and then annually.

Assessment of Cardiac Function

We measured right and left ventricular ejection fractions (RVEF and LVEF) by radionuclide ventriculography, which was performed by a bolus injection of technetium Tc 99m. For determination of RVEF, a gated first-pass study was performed at rest. LVEF was measured by the equilibrium method. Radionuclide ventriculography was performed before transplantation, at 2 months, 6 months, and then annually after transplantation for PAH patients. It was performed before transplantation, at 2 months, and 6 months after transplantation for non-PAH patients.

Pulmonary hemodynamics was measured by a right heart catheter examination using a Swan-Ganz catheter (Edwards LifeSciences, Irvine, Calif). Cardiac output was calculated by the Fick equation, thermodilution technique, or both. Right heart catheterization was performed before transplantation, at 2 months, 1 year, and 3 years after transplantation for PAH patients. It was performed before transplantation and at 2 months after transplantation for non-PAH patients. All data were prospectively collected.

Statistical Analysis

The differences of significance among categorized groups were compared by unpaired Student *t* tests or Fisher's exact tests. Statistical analyses were conducted by StatView 5.0 Program for Windows (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided.

RESULTS

Patient Characteristics

We performed LDLLT in 41 patients between October 1998 and September 2006 at our institution (Okayama). Among the 41 recipients, 39 (95.1%) survived longer than 6 months. Early death occurred in 2 patients (idiopathic interstitial pneumonia and bronchiolitis obliterans after bone marrow transplantation) owing to acute rejection and *Aspergillus* infection, respectively. To simplify the study, we excluded 6 patients from further analysis because of significant secondary pulmonary hypertension (systolic PAP [sPAP] > 65 mm Hg) in 3 patients, small graft size (less than 50% of predicted FVC) in 2 patients, and single lobe transplantation in 1 patient.

Therefore, 33 patients were enrolled in this study. These patients were divided into two groups, the PAH group (n = 12) and the non-PAH group (n = 21). The details of patient characteristics are shown in Table 1. Patients in the PAH group were significantly younger than those in the non-PAH group (24.1 ± 3.1 years vs 37.2 ± 2.8 years; $P = .0062$). The estimated graft FVC was similar between the two groups (71.2% ± 4.1% vs 65.3% ± 2.6%; $P = .21$).

The PAH group included patients with idiopathic PAH, pulmonary veno-occlusive disease, and pulmonary capillary hemagiomatosis. All 12 patients in the PAH group were receiving high-dose intravenous epoprostenol (94 ± 14 ng · kg^{-1} · min^{-1}) for 707 ± 163 days at the time of LDLLT. One patient was receiving the oral dual endothelin receptor antagonist bosentan, which became available in June 2005. Eleven patients required inotropic support. The non-PAH group included patients with idiopathic interstitial pneumonia, bronchiolitis obliterans, lymphangioleiomyomatosis, bronchiectasis, cystic fibrosis, and chronic obstructive lung disease.

Postoperative Course

Transient lung edema associated with left ventricular failure occurred in 3 (25%) recipients in the PAH group, but was not seen in any recipients in the non-PAH group early after LDLLT. One patient in the non-PAH group required mechanical ventilation for 121 days owing to bilateral phrenic nerve palsy. Excluding this patient, the duration of

TABLE 1. Patient characteristics

Variables	PAH group (n = 12)	Non-PAH group (n = 21)	*P* value
Female/male	9/3	18/3	.64
Age (y)	24.1 ± 3.1	37.2 ± 2.8	.0062
Graft size (%)	71.2 ± 4.1	65.3 ± 2.6	.21
Diseases			
IPAH	9	0	
PVOD	2	0	
PCH	1	0	
IIP	0	8	
BO	0	5	
LAM	0	3	
BE	0	3	
CF	0	1	
COPD	0	1	

IPAH, Idiopathic pulmonary arterial hypertension; *PVOD,* pulmononary veno-occlusive disease; *PCH,* pulmonary capillary hemangiomatosis; *IIP,* idiopathic interstitial pneumonitis; *BO,* bronchiolitis obliterans; *LAM,* lymphangioleiomyomatosis; *BE,* bronchiectasis; *CF,* cystic fibrosis; *COPD,* chronic obstructive pulmonary disease.

postoperative mechanical ventilation until extubation was significantly longer in the PAH group than in the non-PAH group (16.6 ± 3.8 days vs 7.6 ± 1.5 days; $P < .001$).

As of August 2007, there were 3 late deaths and 30 (91%) of 33 recipients were alive with a mean follow-up period of 4.2 years. One patient with idiopathic PAH died of chronic rejection at 65 months, 1 patient with bronchiolitis obliterans died of encephalitis at 11 months, and 1 patient with idiopathic interstitial pneumonia died of chronic rejection at 31 months after LDLLT.

Comparison of Cardiac Function Between the PAH and Non-PAH Groups

Serial comparisons of RVEF, LVEF, sPAP (mm Hg), and cardiac index (CI) ($L \cdot min^{-1} \cdot m^{-2}$) between the PAH group and the non-PAH group are shown in Table 2. Some of the planned examinations could not be performed because some patients were too sick.

RVEF was significantly lower in the PAH group than in the non-PAH group before transplantation (29.8% ± 7.0% vs 49.7% ± 3.3%; $P = .010$). At 2 months after LDLLT, RVEF in the PAH group improved dramatically and equaled that in the non-PAH group (57.3% ± 5.1% vs 58.3% ± 2.8%; $P = .86$). Interestingly, RVEF became significantly higher in the PAH group than in the non-PAH group at 6 months (65.1% ± 2.4% vs 57.2% ± 2.0%; $P = .020$).

LVEF tended to be lower in the PAH group than in the non-PAH group before transplantation (49.9% ± 6.6% vs 65.2% ± 1.9%; $P = .068$). At 2 months, contrary to the early RVEF recovery, LVEF in the PAH group did not improve and was significantly lower than in the non-PAH group (50.9% ± 3.7% vs 65.4% ± 2.8%; $P = .0038$). At 6 months, the recipients in the PAH group demonstrated a significant rise in LVEF to values similar to those in the non-PAH group (64.1% ± 3.2% vs 63.0% ± 2.4%; $P = .78$).

TABLE 2. Comparison of cardiac function and pulmonary hemodynamics between PAH and non-PAH groups

Variables	PAH group (n = 12)	Non-PAH group (n = 21)	*P* value
Before LDLLT			
RVEF (%)	29.8 ± 7.0 (n = 6)	49.7 ± 3.3 (n = 11)	.010
LVEF (%)	49.9 ± 6.6 (n = 6)	65.2 ± 1.9 (n = 11)	.068
sPAP (mm Hg)	93.1 ± 6.7 (n = 12)	31.4 ± 2.9 (n = 12)	<.0001
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.03 ± 0.12 (n = 12)	3.49 ± 0.24 (n = 12)	<.0001
Two months after LDLLT			
RVEF (%)	57.3 ± 5.1 (n = 11)	58.3 ± 2.8 (n = 14)	.86
LVEF (%)	50.9 ± 3.7 (n = 11)	65.4 ± 2.8 (n = 14)	.0038
sPAP (mm Hg)	25.7± 1.8 (n = 12)	22.4 ± 1.2 (n = 19)	.13
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.66 ± 0.12 (n = 12)	3.13 ± 0.15 (n = 19)	.037
Six months after LDLLT			
RVEF (%)	65.1 ± 2.4 (n = 11)	57.2 ± 2.0 (n = 19)	.020
LVEF (%)	64.1 ± 3.2 (n = 11)	63.0 ± 2.4 (n = 19)	.78

PAH, Pulmonary arterial hypertension; *LDLLT,* living-donor lobar lung transplantation; *RVEF,* right ventricular ejection fraction; *LVEF,* left ventricular ejection fraction; *sPAP,* systolic pulmonary arterial pressure; *CI,* cardiac index.

sPAP was significantly higher in the PAH group than in the non-PAH group before transplantation (93.1 ± 6.7 mm Hg vs 31.4 ± 2.9 mm Hg; $P < .0001$). Both groups showed a significant reduction in sPAP to normal levels at 2 months (25.7 ± 1.8 mm Hg vs 22.4 ± 1.2 mm Hg; $P = .13$).

CI was significantly lower in the PAH group than in the non-PAH group before transplantation (2.03 ± 0.12 $L \cdot min^{-1} \cdot m^{-2}$ vs 3.49 ± 0.24 $L \cdot min^{-1} \cdot m^{-2}$; $P < .0001$). At 2 months, CI in the PAH group improved significantly but was still significantly lower than that in the non-PAH group (2.66 ± 0.12 $L \cdot min^{-1} \cdot m^{-2}$ vs 3.13 ± 0.15 $L \cdot min^{-1} \cdot m^{-2}$; $P = .037$). CI in the PAH group further improved to 3.23 ± 0.20 $L \cdot min^{-1} \cdot m^{-2}$ at 1 year.

The time course changes of RVEF, LVEF, sPAP, and CI are shown in Figure 1. RVEF and sPAP in the PAH group recovered to the levels in the non-PAH group within 2 months after LDLLT. In contrast, recovery of LVEF and CI required 6 to 12 months. In the PAH group, RVEFs at 1, 2, and 3 years were 64.0% ± 3.0%, 66.2% ± 3.1%, and 66.6% ± 3.6%, respectively. LVEFs at 1, 2, and 3 years were 61.4% ± 2.2%, 66.0% ± 3.5%, and 70.9% ± 3.7%, respectively. sPAPs at 1 and 3 years were 26.1 ± 2.7 mm Hg and 22.4 ± 1.4 mm Hg. CIs at 1 and 3 years were 3.23 ± 0.20 $L \cdot min^{-1} \cdot m^{-2}$ and 2.98 ± 0.17 $L \cdot min^{-1} \cdot m^{-2}$, respectively. These results indicated that the improved cardiac function and pulmonary hemodynamics were well maintained for up to 3 years in the PAH group.

DISCUSSION

Isolated lung transplantation, either single or bilateral, has been successfully performed in patients with end-stage

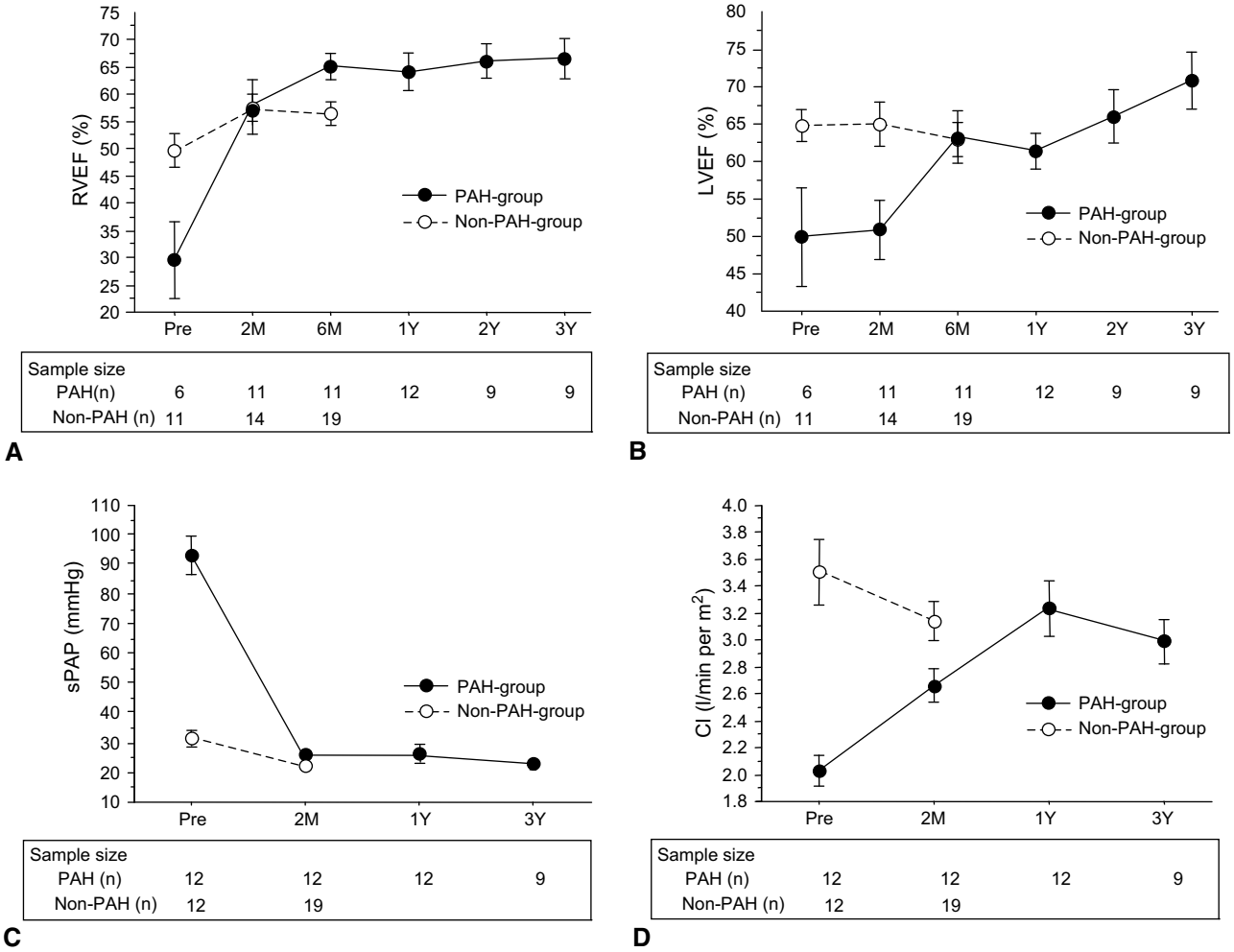

FIGURE 1. The time course changes of RVEF (A), LVEF (B), sPAP (C), and CI (D) after LDLLT. RVEF and sPAP became similar between the PAH group and non-PAH groups at 2 months. In contrast, LVEF and CI were significantly lower in the PAH group than in the non-PAH group at 2 months. At 6 to 12 months, the PAH group showed normal RVEF, LVEF, sPAP and CI. These values continued to be normal for up to 3 years. *RVEF,* Right ventricular ejection fraction; *LVEF,* left ventricular ejection fraction; *sPAP,* systemic pulmonary artery pressure; *CI,* cardiac index; *PAH,* pulmonary arterial hypertension.

PAH.[10-13] Compared with heart–lung transplantation, lung transplantation has the advantage of sparing the recipients' own heart, an important factor considering the scarcity of the available donor pool. However, the recipient's heart has been working against PAH for a certain period of time before transplantation, leading to right ventricular dilatation and left ventricular deformation by septal flattening toward its cavity. A number of studies have shown that right ventricular function and PAP improve dramatically soon after single and bilateral isolated lung transplantation.[10-13] In contrast, changes in left ventricular function have not been well studied.

We began to apply LDLLT to both pediatric[7] and adult[8] patients with PAH. Although a limited amount of lung tissue was implanted, PAP became nearly normal at 2 months, validating the functional capacity of 2 adult lobes to handle the cardiac output of a recipient with PAH. However, we observed frequent transient lung edema associated with left ventricular dysfunction in this group of recipients. The present study was conducted to evaluate time course changes in right and left ventricular functions and pulmonary hemodynamics in patients with PAH receiving LDLLT. To obtain objective data, we used radionuclide ventriculography and right heart catheterization. Echocardiography was not chosen because dramatic geometric changes caused by LDLLT made it difficult to evaluate right and left ventricular functions.

The present study clearly demonstrated rapid recovery of right ventricular function and PAP within 2 months after LDLLT in the PAH group. The better RVEF in the PAH group compared with the non-PAH group at 6 months might be related to the fact that the right ventricle had been ''trained'' by high afterload owing to severe PAH. This result also suggests that the right ventricle is not irreversibly damaged in pump function by enlargement and hypertrophy under high afterload conditions. Previous studies on patients receiving cadaveric lung transplants also demonstrated that

normalization of PAP resulted in remodeling of distorted cardiac geometry regardless of the pre-existing right ventricular enlargement and tricuspid insufficiency.[10-13]

Contrary to the early recovery of right ventricular function, the impaired left ventricular function persisted at 2 months despite findings that left ventricular geometry was restored earlier after reversal of PAH. This finding suggests that factors other than ventricular geometry may play a role. Using Doppler echocardiography, Xie and his colleagues[15] also reported that the left ventricular geometry became more circular; however, impaired early filling persisted after single lung transplantation. Chronic preload reduction may adversely affect the left ventricular compliance and muscle stiffness. Our patients with PAH were receiving full pharmacologic treatment including high-dose intravenous epoprostenol. It therefore can be anticipated that these patients were in a much more debilitated state for a longer period than patients referred for lung transplantation 10 years ago.

Three of the first 6 patients with PAH had transient lung edema associated with left ventricular dysfunction 5, 14, and 28 days after LDLLT, respectively. Lung edema occurred suddenly, and these 3 patients did not show any sign of lung edema before these episodes. Clinical findings demonstrated by echocardiography helped establish the diagnosis of left ventricular dysfunction. This complication has also been reported after conventional bilateral lung transplantation.[16] The withdrawal of mechanical ventilation along with the subsequent increase of venous return and cardiac preload, associated with the augmented work of breathing, may be the cause of the edema. Although postoperative days of left ventricular dysfunction varied, we believe that the pathophysiology of this complication in these 3 patients was similar. All 3 patients responded to therapy including steroid pulse, inotropic drugs, afterload reduction with vasodilators, and nitric oxide inhalation. The last 6 patients with PAH were supported by a ventilator for at least a week and weaned very slowly along with elective tracheostomy. A left atrial line was placed through the left appendage at the time of transplantation, and left atrial pressure was carefully monitored. Inotropes, diuretics, and nitric oxide inhalation were used longer. As a result, none of the last 6 patients with PAH had lung edema. Meticulous postoperative management is mandatory because mild left ventricular dysfunction may easily result in lung edema after LDLLT, in which a limited amount of lung tissue is transplanted.

At 6 months to 1 year, the recipients in the PAH group demonstrated a significant rise in LVEF and CI to the similar values in the non-PAH group measured at 2 months, and these values were stable for up to 3 years. These findings suggest that left ventricular physiologic function can also recover completely and, once it has recovered, it lasts long term.

In conclusion, right ventricular function recovered early after LDLLT for PAH; however, recovery of left ventricular function required 6 to 12 months. The high incidence of lung edema early after LDLLT may be partially related to the dissociation between physiologic and geometric recovery in left ventricular function. Improved cardiac function was sustained for up to 3 years, suggesting long-term durability of cardiac function recovery. Excellent prognosis and complete recovery of right and left ventricular functions support the option of LDLLT for patients with severe PAH.

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